INFECTION

HERAKLES and the Kēres

see over

SCARLET FEVER

TYPICAL RASH

HERAKLES AND THE KĒRES *(see cover)*

Herakles, the Greek Hero-God, in his healing aspect, triumphs particularly over disease in the form of Kēres or tiny spirit-beings, which may well be likened to bacteria, for the *Kēr* was looked upon as the disease itself and not as a personification.

Herakles is depicted in art as beating off the small figures.

INFECTION

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INTRODUCTION

Of recent years the most notable advances in the treatment of bacterial diseases have undoubtedly been the introduction of refined sera and the sulphanilamide group of drugs.

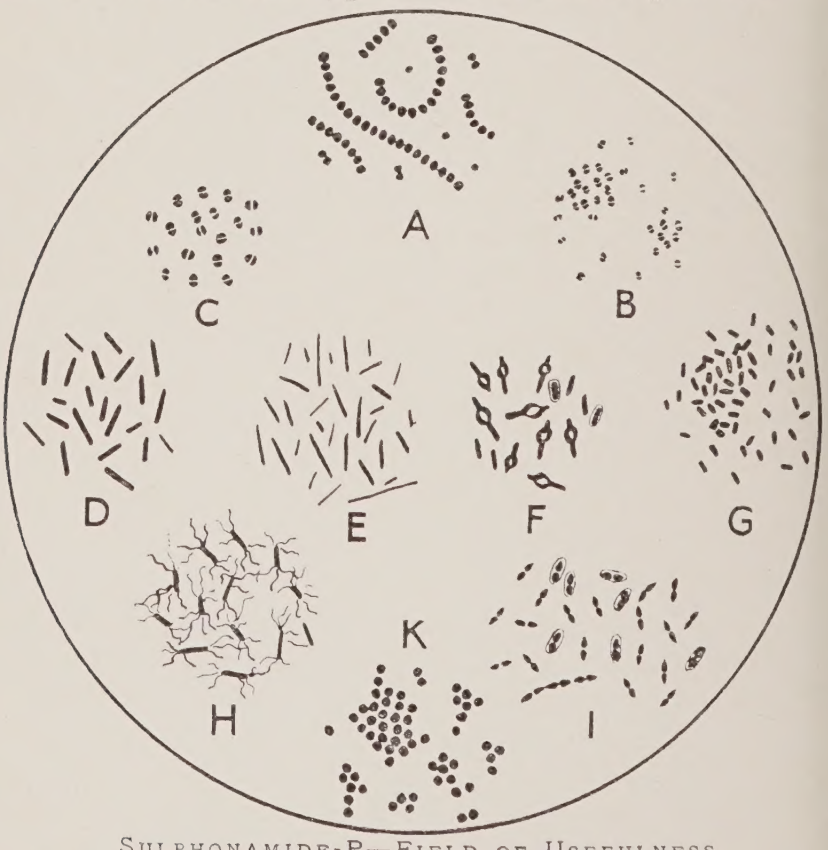
Value of Refined Sera

The introduction of "refined" antitoxins, prepared by selected treatment with proteolytic enzymes with modification of the residual globulin, marks a further important advance in lessening the incidence of serum sickness. The volume to be injected is still further reduced. For the same number of units refined serum contains less than half the amount of protein present in the concentrated sera hitherto used. The antitoxin-bearing molecule is smaller, a property which appears to be connected with the apparently low liability of refined antitoxin to cause serum sickness and also with the greater efficiency of the serum.

Printed in England

Sulphonamide-P

The discovery by Domagk that two azo-dyes prevented the development of streptococcal septicæmia in mice led to a large amount of work on the chemotherapy of bacterial infections. Both these azo-dyes contained a nucleus known as *p*-aminobenzenesulphonamide. It was later shown in a series of preparations that, whereas any alteration of the *p*-aminobenzenesulphonamide nucleus produced an inactive compound, the structure of the remainder of the molecule could be altered without destroying the streptococcicidal activity. The effect of the nucleus itself, *p*-aminobenzenesulphonamide



SULPHONAMIDE-P—FIELD OF USEFULNESS

The accompanying diagram gives some idea of the wide variety of bacteria acted upon, or claimed to be acted upon, by sulphanilamide. (A) streptococci; (B) meningococci; (C) gonococci; (D) *Bact. coli;* (E) *Proteus Ammoniæ;* (F) *Cl. welchii;* (G) *Br. abortus;* (H) *Bact. typhosum;* (I) pneumococci; and (K) staphylococci.

(now generally referred to as sulphanilamide or sulphonamide-P), was then tried and subsequent investigations established the value of this drug in combating a number of bacterial infections. Clinical evidence is available of the usefulness of sulphanilamide in streptococcal, meningococcal, gonococcal and urinary tract infections.

In addition to the recent advances outlined above, there remain to be described several products of note, the therapeutic value of which has long been established.

Bacterial Vaccines

Bacterial vaccines act by producing an active immunity to the corresponding living organisms. The cells of the body are stimulated by the introduction of the inoculum to form specific antibodies. This production of antibodies goes on for a considerable time after inoculation, and the resistance thus acquired lasts longer than the passive immunity due to the injection of immune sera. Unlike the latter, however, vaccines do not confer immediate protection. Though it is possible in carefully-adjusted laboratory experiment to show the production of a "negative phase" following the injection of varying quantities of vaccine, it is generally accepted that this is seldom of importance in practice.

Neoarsphenamine and Sulpharsphenamine

The introduction of organic arsenical compounds in the treatment of syphilis and other diseases was of great practical importance in clinical medicine. 'KHARSIVAN' (Arsphenamine) was the first British product to be issued. The discovery of neoarsphenamine was an even greater advance and this substance has now become the standard means of treatment of syphilis.

'NEOKHARSIVAN' (Neoarsphenamine) and 'KHARSULPHAN' (Sulpharsphenamine) are

manufactured by Burroughs Wellcome & Co. and are approved by the Ministry of Health for use under the Public Health (Venereal Diseases) Regulations. They comply with the requirements of the Therapeutic Substances Act (Great Britain), 1925 (1931 Regulations), and of the B.P. 1932.

Bismuth and Mercury

In the treatment of venereal diseases bismuth and mercury must also continue to find a place. It has been suggested, in explanation of the spirochæticidal action of bismuth, that the element bismuth combines with the tissues to form a complex organic compound which has been named "bismoxyl," and that this compound exerts a specific action against the *Treponema pallidum*. The cellular element which is presumed to enter into "bismoxyl" is present in most tissues, but not in blood. Injections of bismuth, therefore, should be intramuscular, and the injection mass introduced deeply into the tissues.

Mercury was, of course, one of the first drugs to be used as a specific disinfectant and employed as a remedy for syphilis, but satisfactory results may only be obtained if there is an adequate concentration of the drug in the blood-stream, and the difficulty therefore is to maintain this necessary concentration over a long period without producing toxic effects.

DIPHTHERIA

Prophylaxis—Active Immunity

Three types of prophylactics (A.P.T., T.A.F., T.A.M.) are issued, all prepared from diphtheria toxin rendered harmless by formalin and heat (*i.e.*, Formol-Toxoid F.T.).

The injection is usually made intramuscularly or subcutaneously deeply into the arm, above the insertion of the deltoid. (It is wise to warn against active use of the arm for the remainder of the day,

and where convenient, to inject just before bedtime.) With all these prophylactics, 80 to 100 per cent. of subjects will be found Schick-negative within six weeks of the final injection; the percentage varies in different groups, being higher amongst the Schick-positive children where the natural Schick-negative rate is high. Persons who are still Schick-positive after injections of prophylactic should receive further immunisation. A Schick-negative result after a course of prophylactic, implies a useful level of circulating antitoxin which gives almost complete protection against diphtheria and lasts, in all but a small percentage of people, for some years.

Diphtheria, almost invariably mild, has been reported from time to time in Schick-negative reactors. It is well, when signing "certificates" of immunised children, to include a warning that, notwithstanding immunisation, a "sore throat" should immediately be seen by a doctor; this course provides against error and misunderstanding, and safeguards the small percentage of "immunised" people whose immunity does not persist at a sufficiently high level.

CORYNEBACTERIUM DIPHTHERIÆ

Most city children less than nine months old are maternally immune and do not need immunisation, nor do they respond well to it.

Children between nine months and eight years old are mostly non-immune and rarely suffer from "reactions" after immunisation. Up to this age, one may therefore omit the Schick test and immunise all these children. In older children it is

wise to do a preliminary Schick test. Some workers give scarlet fever prophylactic and diphtheria prophylactic together, making the mixture in the syringe immediately before injection.

The choice of prophylactic depends on (*a*) the amount of testing and supervision available, (*b*) the fear of "reactions," (*c*) the rapidity of immunity desired.

The interval between the injections is of considerable importance, the best results being obtained when some weeks elapse between doses. When possible or convenient the interval should be four weeks, but three weeks is preferable to the shorter period of one week formerly used. When three doses are used the interval between second and third injections need not be longer than two weeks.

	Immunising Efficiency	Liability to Cause Reactions	Dosage
A.P.T.	Very high	Low, especially in young children	2 doses, each of 0·5 c.c.; or 0·1 c.c. and 0·5 c.c. *(see text)*
T.A.F.	High	Very low at all ages	3 doses of 1 c.c.
T.A.M.	Moderate	Low, especially in young children	,,
F.T.	High	Low only in young children	,,

A.P.T. (Alum Precipitated Toxoid)

A suspension of the washed precipitate produced by the addition of alum to toxoid. The discovery that A.P.T. is a prophylactic of extraordinarily high immunising power in animals was made in The Wellcome Physiological Research Laboratories in 1926; its use in human preventive medicine was referred to in 1931. This high immunising efficiency probably depends on the deposition of the relatively insoluble aluminium-toxoid complex at the site of injection and its gradual liberation. A small amount of local tissue reaction may occur—which may be an essential factor in the excellent

immunisation which usually results—and a small painless nodule may form and gradually disappear. In most large collections of figures, a very small number of local sterile "abscesses," healing rapidly after incision, are noted. Recent investigations in The Wellcome Physiological Research Laboratories have made it possible to maintain a high "Lf" content while keeping the nitrogen and aluminium content low. Some guide to the liability of individual patients to suffer from undue reaction during immunisation can be obtained from the response to the injection of the Schick control fluid. Patients who show a clear pseudo-reaction one or two days after the Schick test, will suffer from less reaction with T.A.F. than with A.P.T.

Much has been claimed in some quarters for the efficiency of one injection, but one dose of 0·5 c.c. of A.P.T. of proved high antigenic value may fail to give a high conversion rate unless the natural Schick-negative rate in the group is high, e.g., after a recent epidemic in an institution. For general use two spaced doses give much better results, the conversion to the Schick-negative condition usually being well over 90 per cent. For children under eight, a first dose of 0·5 c.c. may be used which very rarely causes troublesome reactions. A second dose of 0·5 c.c. is given four weeks later. For older children and adults a first dose of 0·1 c.c. has been widely used. This "detects" an unusually sensitive person who may show some local reaction. For these subjects the further immunisation may be two further doses of 0·1 c.c. of A.P.T. (or 1 c.c. of T.A.F.) at intervals of two to four weeks. For those showing no reaction after the first injection a second dose of 0·5 c.c. may be given three to four weeks later.

A.P.T. is usually injected intramuscularly.

T.A.F. (Toxoid-Antitoxin Floccules)

A suspension of the precipitate of floccules formed when toxoid and antitoxin are mixed in appropriate neutralising amounts. This is the least likely of all prophylactics to cause reaction, and is much used for the immunisation of adults.

T.A.M. (Toxoid-Antitoxin Mixture)

The toxoid is diluted and partially neutralised by antitoxin. This is a less efficient prophylactic than any of the others, and is not used so much as formerly.

F.T. (Formol-Toxoid)

Is still much used on the Continent (Ramon's anatoxine) and in Canada. It is diphtheria toxin detoxicated by the action of formalin and heat. From it the other three prophylactics are prepared. It has high immunising efficiency, but unfortunately tends to cause severe reactions particularly in older subjects, and has been largely replaced in this country by T.A.F. (for adults) and A.P.T. (for children).

Re-inoculation with Prophylactic.—Some individuals who have once been Schick-negative relapse to the positive state and have little or no circulating antitoxin in their blood; thus, it may happen that in an institution, trouble may arise from cases of infection, which are generally mild, in subjects previously immunised. When circumstances indicate that a more durable immunity is needed, this can be achieved by periodic re-injections of diphtheria prophylactic. Thus, children who have been immunised in infancy with two doses of A.P.T. might receive a third injection of prophylactic just prior to the beginning of school life. Alternatively, a third dose might be given if there is evidence that a severe wave of infection is occurring locally.

Storage.—The optimum temperature for storage of diphtheria prophylactics is 4° C. It is important that they should not be frozen solid, since deterioration may then be rapid.

When stored in a cool, dark cupboard, prophylactics retain their potency very well. Except in an emergency, however, they should not be used after the date on the label.

Passive Immunity—Refined Diphtheria Antitoxin

Refined Diphtheria Antitoxin is valuable for prophylactic purposes, but the passive immunity produced by the injection is of a temporary nature only, lasting, on the average, from two to three weeks. The antitoxin is destroyed in the body or excreted.

Treatment.—Refined Diphtheria Antitoxin should be given at the earliest possible moment and, preferably, in one adequately large dose.

Neither the initial administration of antitoxin nor the repetition of the dose, should ever be delayed for the result of a bacteriological examination.

The effect of the serum is most rapidly obtained by intravenous injection; the antitoxin then comes into action almost immediately. In the treatment of urgent cases, therefore, a dose of 10,000 to 40,000 units or more should be administered intravenously. The practice of some authorities is to give part of the serum intravenously and part intramuscularly. If intravenous injection is not possible, the serum should be given intramuscularly; it is then much more rapidly absorbed than when given subcutaneously. If the serum is to be given intramuscularly or subcutaneously the dose for a case of moderate severity, seen early in the disease, should never be less than 8000 units, and in more severe cases 20,000 to 50,000 units at least should be given at once. It may be necessary to repeat the dose on the second and third days of treatment. Large doses are essential, in ordinary cases of diphtheria, if the first dose of antitoxin is delayed until after the second day. These doses should be given irrespective of age, because the case-mortality rate from diphtheria in young children is high.

Some authorities recommend that serum should be given intraperitoneally, when intravenous injection is difficult but desirable. Alternatively, the route selected in infants, before the closure of the anterior fontanelle, may be the superior sagittal sinus.

4000 Ehrlich units are contained in 1 c.c. or less of Refined Serum (except phials of 500, 1000 and 2000 units, the volume of which is adjusted by dilution to 1 c.c. or less for convenience in use).

PREPARATIONS

Schick Test Products

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, *Diluted Toxin (Test) and Heated Toxin (Control)
Control and Diluted Toxin Sets of 1 c.c., 5 c.c. and 10 c.c.

For Prophylaxis

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, Diphtheria Prophylactic A.P.T. Alum Precipitated Toxoid for Active Immunisation
Containers of 0·5 c.c., 1 c.c. and 5 c.c.

,, Diphtheria Prophylactic T.A.F. Toxoid-Antitoxin Floccules (Suspension) for Active Immunisation
Containers of 1 c.c., 10 c.c. and 25 c.c.

,, Diphtheria Prophylactic T.A.M. Toxoid-Antitoxin Mixture for Active Immunisation
Containers of 1 c.c., 5 c.c., 10 c.c. and 25 c.c.

Serum

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, Refined Diphtheria Antitoxin—Globulins

Containers of	500	Ehrlich	Units	in 1 c.c. or less
,, ,,	1000	,,	,,	
,, ,,	2000	,,	,,	
,, ,,	4000	,,	,,	
,, ,,	5000	,,	,,	4000 units or more per c.c.
,, ,,	6000	,,	,,	
,, ,,	8000	,,	,,	
,, ,,	10,000	,,	,,	
,, ,,	20,000	,,	,,	
,, ,,	40,000	,,	,,	

* *Supplied in Great Britain, Northern Ireland and Eire only*

STREPTOCOCCAL INFECTIONS

Scarlet Fever

Prophylaxis

The results obtained in various hospitals demonstrate that by testing, and, where necessary, actively immunising the nurses, scarlet fever amongst them is reduced to the point of disappearance, and immunisation of children and others liable to be exposed to infection is coming into more general use. Some writers advise the immunisation of family contacts immediately after the infected child has been removed to hospital, believing that the contacts may become immune before the convalescent child returns from hospital. In an epidemic in a school or institution the "Dick negative reactors" can be regarded as immune against scarlet fever.

STREPTOCOCCI

Scarlet Fever Prophylactic for Active Immunisation

Toxin is issued in two strengths:—

A. Containing 2500 skin test doses per c.c.

D. Containing 50,000 skin test doses per c.c.

The immunising course consists of four or five weekly subcutaneous or intramuscular injections of a scarlet fever toxin which contains no blood or serum. The Dicks recommend superficial subcutaneous injections given "near enough the under surface of the skin to produce a visible subcutaneous

lump.'' They claim that this technique is helpful in avoiding both severe local and severe general reactions.

Dosage is cautious as it is toxin which is used. If necessary, doses which cause no reaction may be repeated after an interval of a few days, provided that an interval of at least two to three weeks occurs between the last two doses of the course.

Most workers are agreed that a first injection of 500 or even 1000 doses rarely causes a reaction (except in those with a vivid positive Dick response). There is no general agreement as to the best dosage thereafter. The tendency in this country is to give a total of 80,000 to 100,000 skin test doses in four or five injections. Sequence I represents the average practice of those who favour large doses and expect high immunity at the cost of a certain percentage of ''reactions.'' (It has been stated that the inoculation of 0·2 c.c. of adrenaline solution in each dose materially reduces the incidence of reactions in those prone to them.)

Sequence I

500 = 0·2 c.c. Strength A
2000 = 0·8 c.c. Strength A
5000 = 0·1 c.c. Strength D
25,000 = 0·5 c.c. Strength D
50,000 = 1 c.c. Strength D

Some physicians would choose a shorter sequence such as, 1000, 5000, 10,000 (or 20,000). A good working compromise, particularly in residential schools, would consist in giving the first three (or perhaps four) injections of Sequence I, and Dick testing one to two weeks later; those children still positive would continue injection.

The Dicks recommend the following sequence :— 650, 2500, 10,000, 30,000 and 100,000 to 120,000 skin test doses. They suggest an injection of one-quarter or one-half the usual first dose as a preliminary in persons who are highly susceptible as shown by large bright skin reactions.

The majority of those inoculated become negative within a few weeks. It is not yet known with certainty how long the immunity lasts. It is probably wise to Dick test those specially exposed, e.g., nurses, every six or twelve months, and to give injections of prophylactic to those who are positive.

If an excessive dose of prophylactic is given in the earlier stages of immunisation, the patient may show what has been called "the scarlatinoid syndrome," namely, a generalised rash with malaise or vomiting. Such symptoms are very rarely observed as a result of the usual course of immunisation; they disappear in 24 to 48 hours, and need not cause undue alarm. (It is probable that the patient will become more rapidly immune if the dose has been large enough to cause this syndrome.)

N.B.—Syringes and needles used for injection of scarlet fever toxin should be sterilised by dry heat, in the autoclave, or by boiling in distilled water. Alcohol or other disinfectants which may precipitate the toxin should be avoided.

Passive Immunity—Refined Streptococcus Antitoxin (Scarlatina)

Passive immunisation has been found of use when scarlet fever has occurred in general wards in children's hospitals, schools and institutions, and amongst diphtheria convalescent patients. All the contacts are examined by the Dick test and those

giving a positive reaction are immediately protected with antitoxin. The usual dose is 3000 U.S.A. units which will turn most "Dick-positive reactors" negative within 24 hours and keep the reaction negative for some days. Some clinicians prefer to give 1500 U.S.A. units. Clinical experience has shown that by this method the majority of contacts can be efficiently protected against streptococcal toxin. It should be remembered, however, that they are still susceptible to tonsillitis, etc., and may have to be isolated.

Some authorities recommend that if the chances of contracting scarlet fever are not high, active immunisation should be chosen in preference to the administration of serum.

Treatment—Refined Streptococcus Antitoxin (Scarlatina)

In scarlet fever the antitoxin, given early and in proper dosage, has an obvious curative effect. In the average patient the temperature falls rapidly and the clinical condition is much improved within a few hours of the administration of the serum. Many clinicians believe that the incidence of serious complications is also reduced, but this view is not universally accepted. The probability is that the antitoxin, by enabling the patient to overcome the toxæmia, allows the natural defences of the body to combat the pyogenic or septic complications. Some of the leading immunologists hold the view that scarlet fever antitoxin is effective only against the erythrogenic toxin, and therefore is of little or no use in fevers without rash, e.g., septicæmia, puerperal fever, tonsillitis, etc. Some clinicians do not hold this view and use antitoxin

in all conditions which are certainly or probably caused by hæmolytic streptococci, and believe that they obtain good results by so doing.

Many physicians do not give serum to mild cases of scarlet fever, preferring to avoid the risk of serum sickness. If it is thought advisable to treat mild cases, 3000 U.S.A. units would seem a suitable dose; experience seems to suggest that not less than 6000 U.S.A. units should be given to severe cases, repeated daily if necessary, and from 6000 to 15,000 U.S.A. units to very severe cases. The dose recommended by the Scarlet Fever Committee is at least 8000 U.S.A. units. The serum is given intramuscularly in ordinary cases, and intravenously in very urgent cases. In young children, Banks prefers the intraperitoneal route on account of the relative ease of administration.

Sulphonamide-P (Sulphanilamide)

Sulphonamide-P (Sulphanilamide), either alone or followed by the antitoxin, is being extensively used clinically in the treatment of streptococcal infections, and the available evidence justifies the continuance of this practice, although the drug is believed to have no influence on the primary toxæmia of scarlet fever.

Streptococcal Septicæmia

Whenever there is an indication of the presence of streptococcal infection of the blood-stream, sulphanilamide may be administered with advantage. The usual dose is up to six to eight grammes (one gramme per 20 lb. body-weight for adults) by mouth per diem, until the temperature has fallen, then diminished to one to two grammes continued for at least a week.

Erysipelas

The value of sulphanilamide in the treatment of erysipelas is now established. Clinical reports are numerous, and the evidence indicates that since the introduction of sulphanilamide therapy the case fatality rate has been markedly reduced. It has been shown that in a large number of cases the spread of the lesion is stopped within 24 hours, the temperature returns to normal within 48 hours, and within 72 hours the toxæmia of the disease disappears. The dosage suggested for adults is one gramme every four hours, *i.e.*, six grammes a day until cure is established; thereafter one gramme three times daily for a further period of 14 days. In the case of children, the dose should be calculated on body-weight. Banks states that children require 50 per cent. more than adults per unit of body-weight, and infants require three times as much on a similar basis.

Tonsillitis and Ludwig's Angina

Sulphanilamide is of value in cases of acute follicular tonsillitis, which responds readily to the treatment. A fall of temperature by crisis within 24 hours is not unusual, but it is advisable to continue the treatment for three days to avoid relapse. The usual dose for an adult is one gramme thrice daily, but if the bacteriological investigation proves to be negative for the hæmolytic streptococci the drug should be discontinued.

PREPARATIONS

Dick Test Products

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, ***Diluted Scarlet Fever Toxin (Test) and Heated Scarlet Fever Toxin (Control)**

Test and Control Sets of 1 *c.c. and* 5 *c.c.*

* *Supplied in Great Britain, Northern Ireland and Eire only*

For Prophylaxis

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, *Scarlet Fever Prophylactic (A) for Active Immunisation
Containers of 1 *c.c.*, 10 *c.c. and* 25 *c.c., containing* 2500 *skin test doses per c.c.*

,, *Scarlet Fever Prophylactic (D) for Active Immunisation
Containers of 1 *c.c.*, 10 *c.c. and* 25 *c.c., containing* 50,000 *skin test doses per c.c.*

For Treatment

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, Refined Streptococcus Antitoxin (Scarlatina)—Globulins
Containers of 3000 *and* 10,000 *U.S.A. Units*
1000 *U.S.A. Units or more per c.c.*

'TABLOID' BRAND—
(Trade Mark)

,, **Sulphonamide-P**, 0·5 gramme *(For Oral administration)*
[SEE LIST B. W. & Co.]

In hæmolytic streptococcal infections, including puerperal fever, and in meningococcal infections, the usual dose is up to 6 to 8 grammes (one gramme per 20 lb. body-weight), by the mouth, per diem, until the temperature has fallen, then diminished to 1 to 2 grammes continued for at least a week. In the treatment of erysipelas the adult dosage is 1 gramme every four hours, *i.e.*, 6 grammes a day until cure is established; thereafter 1 gramme three times daily for a further period of 14 days. Children require 50 per cent. more than adults per unit of body-weight, and infants require three times as much on a similar basis. In urinary infections, the suggested dose is 0·5 gramme, three or four times daily for five days. In gonorrhœa the average length of treatment, *reactions being carefully observed*, is 14 days. Five grammes on each of the first two days in divided doses after each meal and at bedtime; 3·5 grammes daily during the next three days; the final dosage being 2·5 grammes each day for four to eight days, until the urine is clear and the patient is asymptomatic. The prostatic secretion should also be free from gonococci, both by smear and culture.

Bottles of 25 *and* 100

'WELLCOME' BRAND—
(Trade Mark)

,, **Sulphonamide-P** *(For Parenteral or Oral administration)*
[SEE LIST B. W. & Co.]

In hæmolytic streptococcal infections, including puerperal fever: Orally, as a powder or in solution, 6 to 8 grammes daily; parenterally, 0·5 gramme of 'Wellcome' Sulphonamide-P should be boiled in 40 c.c. of saline and cooled to body-temperature before injecting.

It should be realised that this procedure will not kill bacterial spores. Care should therefore be taken in preparing the substance for injection. All syringes, bottles, test tubes, etc., used for injecting the solution should be reserved solely for "clean" products; they should never have been in contact with pus or other infected material.

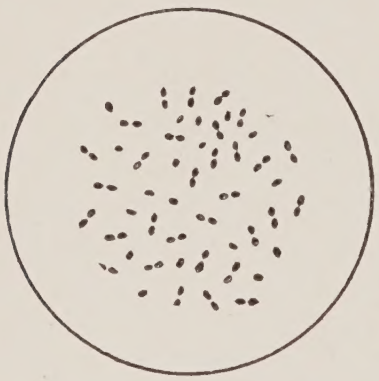
Bottles of 25 *grammes and* 100 *grammes*

* *Supplied in Great Britain, Northern Ireland and Eire only*

WHOOPING COUGH

Contradictory claims are made for the efficiency of whooping cough vaccine, but it offers at present the only hope of protection.

This vaccine is prepared from recent strains of *Hæmophilus pertussis (B. pertussis)* (the Bordet-Gengou bacillus) isolated by the cough-plate method, and in the smooth virulent phase 1. The cultures are grown on Bordet-Gengou medium and are killed by antiseptic. Only one strength is issued, viz., 10,000 million organisms per c.c. There is no satisfactory laboratory test for potency, nor does the clinical evidence yet provide complete proof that all the batches of vaccine made in different parts of the world are effective in prophylaxis. There is no general agreement that vaccine is effective in treatment.



HÆMOPHILUS PERTUSSIS

Since whooping cough is most serious during the early years of life, it is advisable to immunise during infancy, preferably between the 7th and 10th months. It is suggested that a period of several months must elapse before the resulting immunity is complete, but some observers believe that a useful degree of immunity can be obtained in a much shorter period.

Authorities differ as to dosage for prophylaxis. The following dosage, given subcutaneously, is less tedious than some of the courses which have been recommended, although it entails five injections.

The first dose is 1 c.c., given into the left biceps, followed by 1·5 c.c. into the right triceps, to be followed again by 1·5 c.c. into the left triceps; finally 3 c.c. are given (1·5 c.c. into each deltoid). Total = 7 c.c. (equivalent to 70,000 million organisms). The injections may conveniently be given at intervals of one week. Reactions appear to be somewhat more troublesome than in anti-diphtheria immunisation, especially in older children.

Recent investigations suggest that much smaller doses, e.g., 0·5 c.c. or 5000 million organisms, afford satisfactory protection if the interval between injections is from two to four weeks. Three fortnightly doses may be given, followed by a fourth after one month. If persons who have received this course of vaccine are exposed to infection, their immunity may be re-inforced by one further injection of vaccine.

There seems little evidence to justify the use of vaccine for treatment, but some clinicians recommend six subcutaneous injections, each ranging from 100 million to 1000 million organisms, administered on alternate days. Others suggest 1000 million to 3000 million for older children, increasing to 5000 million or more organisms in six injections; smaller doses are stated by these workers to be less effective.

PREPARATIONS

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, **Whooping Cough Vaccine** *(H. Pertussis)*

10 *c.c. containing* 10,000 *million organisms in each c.c.*

GONORRHŒA

Sulphonamide-P

A very large number of papers on the clinical treatment of gonorrhœa with sulphanilamide have appeared. The average length of treatment described is ten days. Five grammes of sulphanilamide are administered on each of the first two days in divided doses after each meal and at bedtime; 3·5 grammes are given daily during the next three days; the final dosage is 2·5 grammes each day for the next four to eight days until the urine is clear of gonococci and the patient is asymptomatic. The prostatic secretion should also be free from gonococci, both by smear and culture. Fluids are not forced, in order that the drugs may be eliminated as slowly as possible in the urine.

Delaying treatment in acute cases tends to increase the number of complications and most authorities prefer to start treatment at once.

After sulphanilamide treatment there is more difficulty in deciding when cases are cured than there was with the older methods. Symptoms disappear rapidly and patients are liable to assume that they are cured when they are in fact still infectious. A rigorous examination for the organism by staining, and if possible culture, of the prostatic secretions is essential. Pelouze emphasises the importance of adequate tests and points out that in determining the cure of gonorrhœa great care must be exercised.

Recently it has been stated of cases treated with Sulphanilamide and which have passed tests for cure, about 20 per cent. relapse after from six months to two years and require re-treatment.

'Tabloid' Sulphonamide-P, 0·5 gramme, is suitable for this medication and may be administered as follows:—10 products daily for

the first two days; 7 products daily for the next three days; 5 products daily during the final four to eight days. When using such a high scale of dosage, it is essential that special watch be kept for toxic effects.

Gonococcus Vaccine

This vaccine, prepared from the *Neisseria gonorrhœæ (Gonococcus)*, has been used in the treatment of the chronic and later stages of gonorrhœa, in gonorrhœal prostatitis, and in generalised gonorrhœal infections, such as gonorrhœal arthritis. It has been employed in cases of chronic gonococcal iritis, but here extreme caution is necessary. Very small doses, e.g., 0·5 to 1 million cocci, are mentioned.

GONOCOCCI IN PUS

The initial dose given by different authorities varies considerably, being, according to some, as high as half a million organisms. Subsequent dosage is regulated in accordance with the constitutional effect.

PREPARATIONS

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, **Gonococcus Vaccine**

1 c.c.	containing	5	million	organisms
1 c.c.	,,	20	,,	,,
1 c.c.	,,	200	,,	,,
1 c.c.	,,	1000	,,	,,

Also containers of 10 *c.c. and* 25 *c.c. (obtainable in the British Empire Overseas to special order only)*

'TABLOID' BRAND—
(Trade Mark)

,, **Sulphonamide-P**, *see page* 17

SYPHILIS

'Neokharsivan' (Neoarsphenamine)

'NEOKHARSIVAN' is administered by intravenous injection, in about 20 per cent. solution. A fine needle is employed in the syringe. Intramuscular injections are irritating and painful and are, therefore, rarely adopted. Subcutaneous injection should never be used.

Injections are given at weekly intervals. The *maximum* single dose is—for men, 0·9 gm.; for women, 0·75 gm.; children (according to age), 0·15 gm. to 0·3 gm.; infants, 0·02 gm. to 0·05 gm. The dose has, in many cases, to be varied according to the individual patient. Treatment should not be commenced with the maximum doses. The commencing dose in men may be as low as 0·15 gm., rapidly increased to the maximum in successive injections if the patient is tolerant.

In many cases where the disease has been present for over two years, it may be impossible to obtain a negative Wassermann reaction. In such cases artificial production of pyrexia by intravenous injection of Anti-typhoid-paratyphoid Vaccine (T.A.B.), 'WELLCOME' Brand, followed by a further course of 'NEOKHARSIVAN,' may render the Wassermann reaction negative.

The taking of the Wassermann reaction in early and primary cases may be preceded by 14 days' administration of iodides. Iodides ('TABLOID' POTASSIUM IODIDE) should be given in large doses for one week at a time and the course repeated several times in late secondary cases. In resistant, uncured and tertiary cases, and in neuro-syphilis, iodides may be given in four-week courses interpolated between neoarsphenamine ('NEOKHARSIVAN') and bismuth courses. Some observers have stated that the *simultaneous* administration of neoarsphenamine and bismuth (or

mercury) gives more favourable results in preventing the development of neuro-syphilis than alternating courses.

Caution should be exercised when patients exhibit evidence of myocarditis, renal or hepatic disease, arterio-sclerosis, aneurism, aortic regurgitation, angina pectoris, syphilitic disease of larynx, diabetes, advanced disease of the central nervous system, gumma of the brain, tendency to eczema, erythema or urticaria. Pregnant patients and alcoholics also require careful treatment. Caution takes the form of lower individual doses given at midday, on an empty stomach, followed by rest in bed and longer intervals between injections.

TREPONEMA PALLIDUM

Careful watch should be kept in all cases for signs of intolerance, which may be indicated by increasingly severe reactions following each injection, persistent nausea between injections, general malaise, loss of weight, erythema, dermatitis and jaundice.

'Kharsulphan' (Sulpharsphenamine)

'KHARSULPHAN' is suitable for use only by subcutaneous or intramuscular injection, and is preferred in children and in special circumstances.

The dose is dissolved in 1 c.c. or more of saline or sterile distilled water in the barrel of the syringe, and is then ready for immediate use. The dose for each patient must be prepared separately as required, and *on no account be stored or allowed to stand.* 'KHARSULPHAN' is readily soluble, and there need be no delay in preparing individual doses.

Treatment should commence with small doses of 0·15 gramme, given at intervals of two or three days.

As the dose is increased, the interval should be lengthened to seven days and then the same scheme carried out as given under 'NEOKHARSIVAN.' 'KHARSULPHAN' is injected subcutaneously into the loose skin of the scapular region or into the forearm, and intramuscularly into the buttock. Range of doses: Men, 0·15–0·6 gramme; women, 0·15–0·45 gramme; children, 0·15–0·3 gramme; infants, 0·02–0·05 gramme.

Bismuth

Bismuth metal (or its salts), administered by intramuscular injection, exerts a powerful anti-spirochætal effect in the primary, secondary and tertiary stages of syphilis, only slightly less effective than arsphenamine and superior to mercury.

It may be administered in courses of one injection weekly for eight to twelve weeks, till a *minimum* of 2 grammes of bismuth has been given, the courses alternating with courses of neoarsphenamine injections in a series lasting about two years.

Administration should be intermitted if the blue "lead-line" appears at the alveolar margin or if stomatitis ensues.

Mercury

One or more courses of mercury may be given to each case, alternating with the courses of arsphenamine and bismuth. The course may consist of four or five injections, at weekly intervals, of one of the insoluble preparations such as 'WELLCOME' MERCURIAL CREAM, or an injection of a soluble salt, every one, two or three days for 5 or 6 weeks (a *minimum* total of 5 grains of mercury being administered). The insoluble forms of mercury are prepared with a creo-camph base in order to minimise development of pain after the injection. Administration should be intermitted if the blue "lead-line" appears at the alveolar margin or if stomatitis ensues.

PREPARATIONS

'Neokharsivan' Brand Neoarsphenamine
(Trade Mark)

Hermetically-sealed phials of 0·15 *gramme*, 0·3 *gramme*, 0·45 *gramme*, 0·6 *gramme*, 0·75 *gramme and* 0·9 *gramme*

The official dose of Neoarsphenamine is 0·15 gramme to 0·9 gramme by intravenous injection.

'Kharsulphan' Brand Sulpharsphenamine
(Trade Mark)

Hermetically-sealed phials of 0·15 *gramme*, 0·3 *gramme*, 0·45 *gramme and* 0·6 *gramme*

The official dose of Sulpharsphenamine is 0·1 gramme to 0·6 gramme by subcutaneous or intramuscular injection.

'Hypoloid' Brand Bismuth Oxychloride, 0·1 gramme (gr. 1½ approx.), *(Trade Mark)* in 1 c.c.

Suspended in a *Sterile* Isotonic Saline Solution.

DIRECTION.—*For use by Intramuscular Injection.* The suggested commencing dose is 1 c.c., increased to 1·5 c.c.

Rubber-capped bottles of 25 *c.c.*

'Hypoloid' Brand Bismuth Metal, 0·2 gramme (gr. 3 approx.) in 1 c.c. *(Trade Mark)*

Suspended in a *Sterile* Isotonic Glucose Solution.

DIRECTION.—*For use by Intramuscular Injection.* The suggested commencing dose is 1 c.c., increased to 1·5 c.c.

Rubber-capped bottles of 5 *c.c.*, 10 *c.c. and* 25 *c.c.*

'Bicreol' Brand Bismuth Cream
(Trade Mark)

Contains 0·15 gm. Metallic Bismuth in 1 c.c. in a creo-camph base.

DIRECTION.—*For use by Intramuscular Injection.* The suggested commencing dose is 1 c.c., increased to 2 c.c.

Glass jars containing ½ *oz. and* 2 *oz.*

'Wellcome' Brand Mercurial Cream, Blue
(Trade Mark)

Contains 10 per cent. of Metallic Mercury in a creo-camph base.

DIRECTION.—Min. 16 (gr. 1½ of mercury), injected intramuscularly.

Bottles containing 2 *oz.*

'Hypoloid' Brand Grey Oil, 0·1 gramme (gr. 1½ approx.) in 1 c.c. *(Trade Mark)*

A sterile suspension of metallic mercury (10 per cent.) in a neutral fatty base with creosote and camphor.

DIRECTION.—One c.c., injected intramuscularly.

Boxes of 10 *'Hypoloid' ampoules*

'Wellcome' Brand Calomel Cream
(Trade Mark)

Contains 5 per cent. of calomel in a creo-camph base.

DIRECTION.—Min. 16 (gr. ¾ of calomel), injected intramuscularly.

Bottles containing 2 *oz.*

'Hypoloid' Brand Calomel, 0·05 gramme (gr. ¾ approx.) in 1 c.c. *(Trade Mark)*

A sterile suspension of calomel in a neutral fatty base with creosote and camphor.

DIRECTION.—One c.c., injected intramuscularly. The maximum official dose is 20 minims by intramuscular injection.

Boxes of 10 *'Hypoloid' ampoules*

'Tabloid' Brand Hypodermic Mercury Succinimide, gr. $\frac{1}{10}$ (0·0065 gm.) *(Trade Mark)*

Freely soluble in water, does not coagulate albumin, and is less liable than other preparations of mercury to cause irritation or induration.

DIRECTION.—One, dissolved in sterile water, and injected intramuscularly. Potassium iodide must not be administered at any time during the course of injections, owing to the formation of an irritant compound in the tissues.

Tubes of 20

'Avenyl' 2-myristoxy-mercuri-3-hydroxybenzaldehyde *(Trade Mark)*

DIRECTION.—A 0·25 per cent. solution in Hydnocarpus Oil or a 0·5 per cent. saturated solution in 'Moogrol' is injected subcutaneously, commencing with 1 c.c. increased to 4 c.c. or more.

For the treatment of leprosy complicated by syphilis.

Tubes of 1 *gramme*

'Wellcome' Brand Anti-Typhoid-Paratyphoid Vaccine (T.A.B.), *(Trade Mark)* *see page* 32

TETANUS

Prophylaxis—Refined Tetanus Antitoxin—Globulins

As a prophylactic, a subcutaneous injection of 1000 to 3000 International Units* of tetanus antitoxin–globulins is given as soon as possible after the receipt of a wound, especially in areas where tetanus is common. The larger dose is strongly recommended by the Medical Research Council (*British Medical Journal*, April 8th, 1939, *page* 738). The primary injection may be followed, if necessary, by a second prophylactic dose of serum injected seven to ten days after the first dose. The serum is also used prophylactically before operation on healed or partly healed wound tissue. The protection conferred by tetanus antitoxin is at its maximum two or three days after injection, then slowly diminishes, becoming very slight after three weeks.

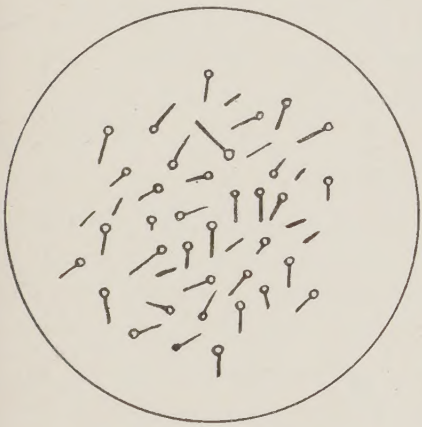
The passive immunity conferred by antitoxic serum may be reinforced by Tetanus Toxoid, giving

*The International Unit which has been accepted in most countries is half the U.S.A. Unit. Thus, 2000 units in the new nomenclature is equal to 1000 units hitherto used in English-speaking countries, *i.e.*, the official U.S.A. Unit. Probably for some years to come both units will be expressed together in English literature.

the first injection two weeks after the dose of serum and the second and possibly third injections at intervals of two to three weeks. It is not considered advisable to begin active immunisation until at least two weeks after the dose of serum because of the slow excretion of the injected antitoxin.

Treatment—Refined Tetanus Antitoxin—Globulins

Therapeutically, the serum should be given in large doses at the earliest possible moment after the diagnosis is evident or reasonably probable. Intrathecally (preferably by the cisterna magna), at least 40,000 International Units, and intravenously, 20,000 to 40,000 International Units (or intramuscularly 20,000 to 100,000 International Units) are given. The dosage of 20,000 to 40,000 International Units may be continued daily until symptoms abate. There is no reason why other treatment considered advisable, such as the liberal use of bromides, chloral, opium, etc., should not proceed simultaneously with the antitoxin treatment.



CLOSTRIDIUM TETANI

Active Immunisation

The toxin of *Clostridium tetani*, rendered atoxic by formalin, *i.e.*, Tetanus Toxoid, has long been employed for immunising animals.

It can be used to produce a high immunity in those persons who may be exposed to tetanus, e.g., in agricultural workers, gardeners and soldiers. In certain tropical regions, in which umbilical

tetanus of infants is common, the disease has been prevented by active immunisation of mothers during pregnancy.

The usual method is to inject two doses of 1 c.c. deeply into the subcutaneous tissues at the back of the left arm. A rather long interval between injections, e.g., six weeks, is favourable to the production of high immunity, though in civil life there may be administrative reasons for choosing four weeks. Reactions after injection are infrequent and almost invariably mild.

Some antitoxin may appear before the second injection, but it rises rapidly during the second week after the second injection to a level which evidence suggests is ample to give a high degree of protection against the risk of tetanus following infected wounds, abrasions, etc.

The active immunity is long-lasting and even when the concentration of antitoxin in the blood is becoming somewhat reduced in the course of time, the patient possesses an active "potential immunity," so that if he is infected with tetanus the antitoxin content of the blood will rise very rapidly.

PREPARATIONS

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, **Refined Tetanus Antitoxin—Globulins**—*For Prophylaxis*
Containers of 1000 *International Units (=*500 *U.S.A. Units) and* 3000 *International Units (=*1500 *U.S.A. Units) in* 1 *c.c. or less and* 10,000 *International Units (=*5000 *U.S.A. Units) and* 30,000 *International Unit (=*15,000 *U.S.A. Units) in* 10 *c.c. or less*

,, **Refined Tetanus Antitoxin—Globulins**—*For Curative Use*
Containers of 20,000 *International Units (=*10,000 *U.S.A. Units)*
8000 *International Units or more per c.c.*

,, ***Tetanus Toxoid for Active Immunisation**
Containers of 1 *c.c. and* 5 *c.c.*

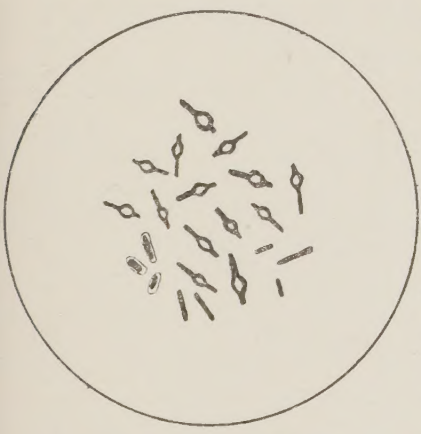
**Supplied in Great Britain, Northern Ireland and Eire only*

GAS-GANGRENE

Refined Gas-Gangrene Antitoxin (Perfringens) —Globulins *(Cl. perfringens=Cl. welchii)*

This antitoxin has been used as a prophylactic against gas-gangrene in grossly infected wounds such as occur in road accidents and in the treatment of gas-gangrene occurring with puerperal sepsis after abortion; also in the treatment of patients with wounds infected with *Cl. perfringens (=Cl. welchii)*.

Its use has also been advocated in abdominal surgery for prophylaxis and treatment of toxæmia of acute intestinal obstruction. It must be admitted that, although the serum has been in general use for several years, there is no full agreement amongst abdominal surgeons on the importance of Welchii toxæmia and the efficiency of the serum. Some are convinced, from repeated clinical experiences, that it has saved their patients; while others, especially in U.S.A., cannot find any experimental or clinical warrant for its use.



CLOSTRIDIUM WELCHII

The suggested dose in soiled wounds is 3000 to 4000 units, given intramuscularly. When the serum is used therapeutically in gas-gangrene, the obvious indication is to give immediately large doses, e.g., 10,000 to 20,000 units intravenously.

Those surgeons who believe in the use of the antitoxin in the treatment of intestinal obstruction give a large dose intravenously and 4000 to 10,000 units daily intramuscularly until the bowels are acting regularly.

Refined Gas-Gangrene Antitoxin—Globulins (Polyvalent)

For Therapeutic Use

The phial contains 7500 units of antitoxin for *Cl. perfringens*, 3750 units for *Cl. septique*, and 2500 units for *Cl. Œdematiens*. These three organisms are those which were identified in actual cases of gas-gangrene in the war of 1914–1918. For treatment the whole contents of the phial should be administered. This is a minimum dose and may be repeated. Since gas-gangrene progresses very rapidly, it is best to administer the antitoxin intravenously, preferably diluted with two volumes of saline and warmed to not above 40° C. If this is not possible, the undiluted material should be given intramuscularly or subcutaneously.

For Prophylactic Use

The phial contains 3000 units of antitoxin for *Cl. perfringens*, 1500 units for *Cl. septique*, and 1000 units for *Cl. Œdematiens*.

PREPARATIONS

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, **Refined Gas-Gangrene Antitoxin (Perfringens)—Globulins**
(Cl. perfringens = Cl. welchii)
Containers of 4000 *International Units and* 10,000 *International Units*
1600 *Units or more per c.c.*

,, **Refined Gas-Gangrene Antitoxin—Globulins (Polyvalent)**
—For Curative Use
Containers of :—

Cl. perfringens	...	...	...	7500 units
Cl. septique	...	...	...	3750 units
Cl. Œdematiens	...	...	...	2500 units

In 10 *c.c. or less*

,, **Refined Gas-Gangrene Antitoxin—Globulins (Polyvalent)**
—For Prophylaxis
Containers of :—

Cl. perfringens	...	...	...	3000 units
Cl. septique	...	...	...	1500 units
Cl. Œdematiens	...	...	...	1000 units

In 4 *c.c. or less*

TYPHOID FEVER

The efficiency of anti-typhoid vaccine in prophylaxis is the best established of all facts concerning the use of bacterial vaccines. Its importance in this respect is amply confirmed by the experiences of the military medical services of all the Great Powers of Europe during the war of 1914–1918. As a result of anti-typhoid inoculation, typhoid fever, instead of being, as in every previous war, one of the most common and most fatal of war diseases, became comparatively rare and unimportant.

BACTERIUM TYPHOSUM

Anti-Typhoid-Paratyphoid Vaccine (T.A.B.)

This vaccine contains *Bacterium typhosum (B. typhosus)* (1000 million per c.c.) and *Bacterium paratyphosum (B. paratyphosus)* A and B (each 750 million per c.c.).

The vaccine is administered subcutaneously, with the usual aseptic precautions. Three doses are usually given at weekly intervals, an average dose being 0·1 c.c., 0·5 c.c., 0·75 c.c.

For those frequently exposed, it is advisable to re-vaccinate with one or two doses every 18 months or two years.

The local symptoms, consisting of redness, swelling, pain and tenderness at the site of injection, begin to appear in two or three hours. Some writers have claimed that these symptoms may be mitigated by the administration of calcium lactate, gr. 30 to gr. 40. Constitutional symptoms—malaise, nausea, headache, etc.—usually disappear within 36 hours. If they are marked, the patient

should be kept in bed for a day after the injection. If the vaccine be given late in the afternoon and no exercise taken thereafter, the chance of reaction is diminished, and if a reaction does occur, it will appear during the night and be less likely to upset the patient. Alcohol in any form should be forbidden for at least 24 hours after vaccination.

Fear of the production of a "negative phase" with lowered resistance has, in the past, sometimes prevented the use of this vaccine during an epidemic. Typhoid vaccine has, however, been used in numerous instances during actual epidemics and has been given to nurses in attendance on typhoid fever cases without any evidence of lowered resistance resulting. Authorities still differ with regard to the advisability of this procedure.

Anti-typhoid vaccine is no longer recommended as a curative agent in typhoid fever.

Anti-Typhoid-Paratyphoid-Cholera Vaccine (T.A.B.C.)

This vaccine contains also *Vibrio choleræ*, the doses and intervals being similar to those mentioned above.

PREPARATIONS

Germ-proof containers

'WELLCOME' BRAND—
(Trade Mark)

,, **Anti-Typhoid-Paratyphoid Vaccine (T.A.B.)**
Containers of 1 *c.c.*, 10 *c.c.** *and* 25 *c.c.**
Containing 1000 million *Bact. typhosum (B. typhosus) and* 750 million each of *Bact. paratyphosum (B. paratyphosus)* A and *Bact. paratyphosum (B. paratyphosus)* B, in each c.c.

,, **Anti-Typhoid-Paratyphoid-Cholera Vaccine (T.A.B.C.)**
Containers of 1 *c.c.*
Containing 1000 million *Bact. typhosum (B. typhosus)*, 750 million each of *Bact. paratyphosum (B. paratyphosus)* A and *Bact. paratyphosum (B. paratyphosus)* B, and 10,000 million *V. Choleræ* (= 4 gm.) in 1 c.c.

**Obtainable in the British Empire Overseas to special order only*

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MEASLES

TYPICAL RASH

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